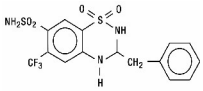
NATURETIN - bendroflumethiazide tablet
APOTHECON

DESCRIPTION

NATURETIN (Bendroflumethiazide Tablets USP) is a benzothiadiazine derivative containing a benzyl and trifluoromethyl group. It is a potent oral diuretic and antihypertensive agent. Bendroflumethiazide is designated chemically as 3-benzyl-3,4-dihydro-6-(trifluoromethyl)-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. Its structural formula is



$C_{15}H_{14}F_3N_3O_4S_2$ MW=421.41

It is available as compressed tablets providing 5 or 10 mg bendroflumethiazide. Inactive ingredients: microcrystalline cellulose, colorants [D&C Yellow No. 10; FD&C Blue No.1 for 5 mg only, and FD&C Yellow No. 6 for 10 mg only], lactose, magnesium stearate, sodium starch glycolate, and pregelatinized starch.

CLINICAL PHARMACOLOGY

Thiazides affect the renal tubular mechanism of electrolyte reabsorption. At maximal therapeutic dosage all thiazides are approximately equal in their diuretic potency.
Thiazides increase excretion of sodium and chloride in approximately equivalent amounts. Natriuresis causes a secondary loss of potassium and bicarbonate.
The mechanism of the antihypertensive effect of thiazides is unknown. Thiazides do not affect normal blood pressure.
Onset of action of thiazides occurs in two hours and the peak effect at about four hours. Duration of action persists for approximately six to 12 hours. Thiazides are eliminated rapidly by the kidney.

INDICATIONS AND USAGE

NATURETIN is indicated as adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy.
NATURETIN has also been found useful in edema due to various forms of renal dysfunction such as: nephrotic syndrome, acute glomerulonephritis, and chronic renal failure.
NATURETIN tablets are indicated in the management of hypertension either as the sole therapeutic agent or to enhance the effectiveness of other antihypertensive drugs in the more severe forms of hypertension.

Usage in Pregnancy.
The routine use of diuretics in an otherwise healthy woman is inappropriate and exposes mother and fetus to unnecessary hazard. Diuretics do not prevent development of toxemia of pregnancy, and there is no satisfactory evidence that they are useful in the treatment of developed toxemia.
Edema during pregnancy may arise from pathological causes or from the physiologic and mechanical consequences of pregnancy. Thiazides are indicated in pregnancy when edema is due to pathologic causes, just as they are in the absence of pregnancy (however, see **PRECAUTIONS, Pregnancy: Nonteratogenic Effects** below). Dependent edema in pregnancy, resulting from restriction of venous return by the expanded uterus, is properly treated through elevation of the lower extremities and use of support hose; use of diuretics to lower intravascular volume in this case is illogical and unnecessary. There is hypervolemia during normal pregnancy which is harmful to neither the fetus nor the mother (in the absence of cardiovascular disease), but which is associated with edema, including generalized edema, in the majority of pregnant women. If this edema produces discomfort, increased recumbency will often provide relief. In rare instances, this edema may cause extreme discomfort which is not relieved by rest. In these cases, a short course of diuretics may provide relief and may be appropriate.

CONTRAINDICATIONS

Bendroflumethiazide is contraindicated in anuria.
It is also contraindicated in patients who have previously demonstrated hypersensitivity to it or other sulfonamide-derived drugs.

WARNINGS

Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.
Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.
Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma.
The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Lithium generally should not be given with diuretics; diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such concomitant therapy.

PRECAUTIONS

General

Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.
All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance, namely: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance may include: dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.
Hypokalemia may develop, especially with brisk diuresis or when severe cirrhosis is present.
Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia can sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Concurrent administration of a potassium-sparing diuretic or potassium supplements may be indicated in these patients.
Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt, except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.
Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy.
Latent diabetes mellitus may become manifest during thiazide administration.
The antihypertensive effect of thiazide diuretics may be enhanced in the post-sympathectomy patient.
If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen (BUN), a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy.
Thiazides may decrease serum PBI levels without signs of thyroid disturbance.
Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid gland with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged thiazide therapy. The common complications of hyperparathyroidism such as renal lithiasis, bone resorption, and peptic ulceration have not been seen. Thiazides should be discontinued before carrying out tests for parathyroid function.
Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia.

Information for Patients

The patient should be advised to take the medication at the same time each day as prescribed to minimize the inconvenience of diuresis, warned against interruption or discontinuation of medication even though he may feel well, and advised about a proper course in the event of an inadvertent missed dose.
The patient should be informed of symptoms that would suggest potential adverse effects and told to report them promptly.

Laboratory Tests

During therapy, the patient's serum electrolyte levels should be regularly monitored. (See **WARNINGS**; **PRECAUTIONS: General**.)

Drug Interactions

When administered concurrently, the following drugs may interact with bendroflumethiazide:
Alcohol, barbiturates, or narcotics–potentiation of orthostatic hypotension may occur.
Amphotericin B, corticosteroids, or corticotropin (ACTH)–may intensify electrolyte imbalance, particularly hypokalemia. Monitor potassium levels; use potassium replacements if necessary.
Anticoagulants (oral)–dosage adjustments of anticoagulant medication may be necessary since bendroflumethiazide may decrease their effects.
Antigout medications–dosage adjustments of antigout medication may be necessary since bendroflumethiazide may raise the level of blood uric acid.
Other antihypertensive medications (e.g., ganglionic or peripheral adrenergic blocking agents)–dosage adjustments may be necessary since bendroflumethiazide may potentiate their effects.
Antidiabetic drugs (oral agents and insulin)–since thiazides may elevate blood glucose levels, dosage adjustments may be necessary.
Calcium salts–increased serum calcium levels due to decreased excretion may occur. If calcium must be prescribed monitor serum calcium levels and adjust calcium dosage accordingly.
Cardiac glycosides–enhanced possibility of digitalis toxicity associated with hypokalemia. Monitor potassium levels; use potassium replacement if necessary.
Cholestyramine resin and colestipol HCL–may delay or decrease absorption of bendroflumethiazide. Sulfonamide diuretics should be taken at least one hour before or four to six hours after these medications.

Diazoxide–enhanced hyperglycemic, hyperuricemic, and antihypertensive effects. Be cognizant of possible interaction; monitor blood glucose and serum uric acid levels.
Lithium salts–may enhance lithium toxicity due to reduced renal clearance. Avoid concurrent use; if lithium must be prescribed monitor serum lithium levels and adjust lithium dosage accordingly. (See **WARNINGS**.)
MAO inhibitors–dosage adjustments of one or both agents may be necessary since hypotensive effects are enhanced.
Nondepolarizing muscle relaxants, preanesthetics and anesthetics used in surgery (e.g., tubocurarine chloride and galamine triethiodide)–effects of these agents may be potentiated; dosage adjustments may be required. Monitor and correct any fluid and electrolyte imbalances prior to surgery if feasible.
Nonsteroidal anti-inflammatory agents–in some patients, the administration of a nonsteroidal anti-inflammatory agent can reduce the diuretic, natriuretic, and antihypertensive effect of loop, potassium-sparing or thiazide diuretics. Therefore, when bendroflumethiazide and nonsteroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.
Methenamine–possible decreased effectiveness due to alkalinization of the urine.
Pressor amines (e.g., norepinephrine)–decreased arterial responsiveness, but not sufficient to preclude effectiveness of the pressor agent for therapeutic use. Use caution in patients taking both medications who undergo surgery. Administer preanesthetic and anesthetic agents in reduced dosage, and if possible, discontinue bendroflumethiazide one week prior to surgery.
Probenecid or sulfinpyrazone–increased dosage of these agents may be necessary since bendroflumethiazide may have hyperuricemic effects.

Drug/Laboratory Test Interactions
Bendroflumethiazide may produce false-negative results with the phentolamine and tyramine tests; may interfere with the phenosulfonphthalein test due to decreased excretion; and it may cause diagnostic interference of serum electrolyte levels, blood and urine glucose levels, and a decrease in serum PBI levels without signs of thyroid disturbance.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Studies have not been performed to evaluate carcinogenic potential, mutagenesis, or whether this drug adversely affects fertility in males or females.

Pregnancy: Teratogenic Effects
Category C. Animal reproduction studies have not been conducted with bendroflumethiazide. It is also not known whether bendroflumethiazide can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Bendroflumethiazide should be given to a pregnant woman only if clearly needed (see **INDICATIONS**).

Pregnancy: Nonteratogenic Effects
Thiazides cross the placental barrier and appear in cord blood. The use of thiazides in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers
Because of the potential for serious adverse reactions in nursing infants from bendroflumethiazide, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness in children have not been established.

ADVERSE REACTIONS
Gastrointestinal: nausea, vomiting, cramping and anorexia are not uncommon; diarrhea, constipation, gastric irritation, abdominal bloating, jaundice (intrahepatic cholestatic jaundice), hepatitis, and sialadenitis occasionally occur; and pancreatitis has been reported.
Central Nervous System: dizziness, vertigo, paresthesia, headache, and xanthopsia occasionally occur.
Hematologic: leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, and aplastic anemia have been reported.
Dermatologic-Hypersensitivity: purpura, exfoliative dermatitis, pruritus, ecchymosis, urticaria, necrotizing angiitis (vasculitis, cutaneous vasculitis), respiratory distress including pneumonitis, fever, and anaphylactic reactions occasionally occur; photosensitivity and rash have been reported.
Cardiovascular: orthostatic hypotension may occur and may be potentiated by coadministration with certain other drugs (e.g., alcohol, barbiturates, narcotics, other antihypertensive medications, etc. (See **PRECAUTIONS: Drug Interactions**.)
Other: muscle spasm, weakness, or restlessness is not uncommon; hyperglycemia, glycosuria, metabolic acidosis in diabetic patients, hyperuricemia, allergic glomerulonephritis, and transient blurred vision occasionally occur.
Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

OVERDOSAGE

Symptoms of overdosage may be manifested in several ways: temporary elevation of BUN; gastrointestinal irritation; and lethargy progressing to coma with minimal depression of respiration and cardiovascular function and without significant serum electrolyte changes or dehydration. Serum electrolyte changes may occur, especially in patients with impaired renal function. The mechanism of thiazide-induced central nervous system depression is unknown.

Treatment is essentially supportive. Evacuation of gastric contents may be useful provided aspiration is avoided in unconscious patients. In conscious patients, induced vomiting using Ipecac Syrup USP is helpful in removing the drug from the stomach. Cathartics should be avoided since they tend to enhance the loss of fluid and electrolytes. Electrolyte levels and renal function should be monitored, and supportive measures instituted to maintain hydration, electrolyte balance, respiration, and cardiovascular-renal function as required. Gastrointestinal irritation is usually of short duration and may be treated symptomatically.

DOSAGE AND ADMINISTRATION

Therapy should be individualized according to patient response and titrated to obtain maximal therapeutic response as well as the lowest dose possible to maintain that therapeutic response and minimize side effects.

Diuretic

The usual dose is 5 mg once daily, preferably given in the morning. To initiate therapy, doses up to 20 mg may be given once daily or divided into two doses. A single daily dose of 2.5 to 5 mg should suffice for maintenance.

Alternatively, intermittent therapy may be advantageous in many patients. By administering the preparation every other day or on a three to five day per week schedule, electrolyte imbalance is less likely to occur; however, the possibility still exists.

In general, the lowest dosage that achieves the therapeutic response should be employed.

Antihypertensive

The suggested initial dosage is 5 to 20 mg daily. Maintenance dosage may range from 2.5 to 15 mg per day depending on the individual response of the patient. When the diuretic is used with other antihypertensive agents, lower maintenance doses for each drug are usually sufficient.

HOW SUPPLIED

NATURETIN® (Bendroflumethiazide Tablets USP)

5 mg/tablet: bottles of 100 (NDC 0003-0606-50).

Each green, round, biconvex tablet with bisect bar is imprinted with identification number 606.

10 mg/tablet: bottles of 100 (NDC 0003-0618-50).

Each orange, round, biconvex tablet with bisect bar is imprinted with identification number 618.

Storage

Dispense in tight containers. Store at room temperature; avoid excessive heat.

APOTHECON®
A Bristol-Myers Squibb Company
Princeton, NJ 08540 USA
1017988A1
Revised August 2000